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A Rare Case of Bilateral Malignant Mixed Mullerian Tumor of Ovary.

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ABSTRACT

Malignant mixed mesodermal tumor (MMMT) of ovary accounts for less than 1% of all ovarian tumors. These aggressive tumors with malignant epithelial and sacromatous elements occur mainly in postmenopausal, low parity women These tumors have aggressive clinical course and very poor prognosis. We herein present a case of malignant mixed mesodermal tumor In a 57 year old postmenopausal woman who presented with complaints of pain and mass per abdomen with loss of appetite and progressive anemia for the last 15 days.There was no history of vaginal bleeding and no relevant past medical history . A large palpable mass in the pelvis was observed during examination. A contrast enhanced CT scan of abdomen revealed a large,complex abdominopelvic mass with multiple omental deposits along with gross ascites.Ascitic fluid cytology reported metastatic ovarian adenocarcinoma.The patient was planned for NeoAdjuvant chemotherapy to be followed by interval cytoreduction surgery and further adjuvant chemotherapy. At approximately 5 months postoperatively, the patient remains alive and recurrence free.

Keywords: Malignant mixed mesodermal tumor, ovary, carcinosarcoma , immunohistochemistry

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INTRODUCTION

Malignant mixed Mullerian tumour (MMMT) of ovary is a rare biphasic malignant neoplasm. It can occur anywhere in the female genital tract , but most commonly affects the uterus. Fallopian tubes, ovaries and the vagina can also be involved. MMMT of the ovary is extremely rare and accounts for about 1-2% of all ovarian malignancies with lesser than 400 cases reported in the literature.[1] The risk factors for MMMTs include nulliparity, obesity long-term tamoxifen use and exogenous oestrogen . A rare exception aside this is a lesion of postmenopausal women.[1,2] MMMT is composed histologically of malignant stromal and epithelial components.Based on the origin of the stromal component ,MMMT can be classified as heterologous or homologous.These tumors are associated with aggressive clinical course and very poor prognosis. Older age at presentation, suboptimal debulking and advanced stage at presentation are poor prognostic indicators[3]

Case Report

A 57-year-old postmenopausal (P_5L_4) woman presented with pain and mass per abdomen with loss of appetite and progressive anaemia for the past 15 days. She also complained of post meal distension, weight loss and easy fatigability. She did not complain of any vaginal bleeding. No relevant past medical history could be elicited. A large pelvic mass was felt on examination. Ultrasound of abdomen and pelvis was suggestive of advanced ovarian carcinoma. Contrast enhanced CT scan revealed a large, complex abdominopelvic cystic lesion with enhancing thin internal septations and enhancing solid component. Multiple omental deposits (especially in the left iliac fossa) scattered in mesentery along with gross ascites were seen. Serum CA-125 was 795 U/ml. Ascitic fluid cytology revealed metastatic adenocarcinoma. Further investigation ruled out distant metastasis. After 3 cycles of NeoAdjuvant chemotherapy with paclitaxel and carboplatin she underwent interval cytoreductive surgery (total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendicectomy and pelvic lymph node dissection) under general anaesthesia. Specimen was sent for histopathological investigation. After this patient underwent one more cycle of chemotherapy and no recurrence has been seen in the 5 month follow-up.

PATHOLOGICAL EXAMINATION

Post-operatively we received hysterectomy specimen with bilateral fallopian tubes and ovaries along with appendix, peritoneum and dissected pelvic lymph nodes.

Gross

Left ovarian mass along with separately sent cyst together weighed 378 gm. Cut section showed a multiloculated cyst measuring 10.8 x 7.5cm and focal papillary areas measuring 6x4cm along with hemorrhagic areas. Right ovarian cystic mass, weighed 212 gm measuring 10x6.5x5cm.Cut section showed grey white areas, multiple papillary areas and focal hemorrhagic areas. Uterus and cervix were free of tumor. Both fallopian tubes were patent. Cervix showed nabothian cyst. No reactive lymph nodes or omental deposits seen.

Microscopic findings

Multiple sections from the left and right ovarian mass showed a tumor composed of infiltrating glands, broad papillae and tubules lined by pleomorphic cells with hyperchromatic nuclei, coarse chromatin with prominent nucleolus, abundant mitosis and scant cytoplasm.(*Fig.1*) Tumor cells arranged in tubules with hobnailing of cells with PAS+ Diastase resistant cytoplasmic globules seen .Surrounding stroma was focally cellular with sheets of cells having hyperchromatic pleomorphic nuclei, coarse chromatin, abundant mitosis with areas of necrosis, heterologous elements with malignant cartilage and osteoid.(*Fig.2*) Foci of lymphoplasmacytic infiltrate, hemosiderin laden macrophages, calcification and hyalinization were noted.

Immunohistochemistry

Tumor cells were focally positive for WT-1 and ER. Tumor cells were diffusely but strongly positive for P53

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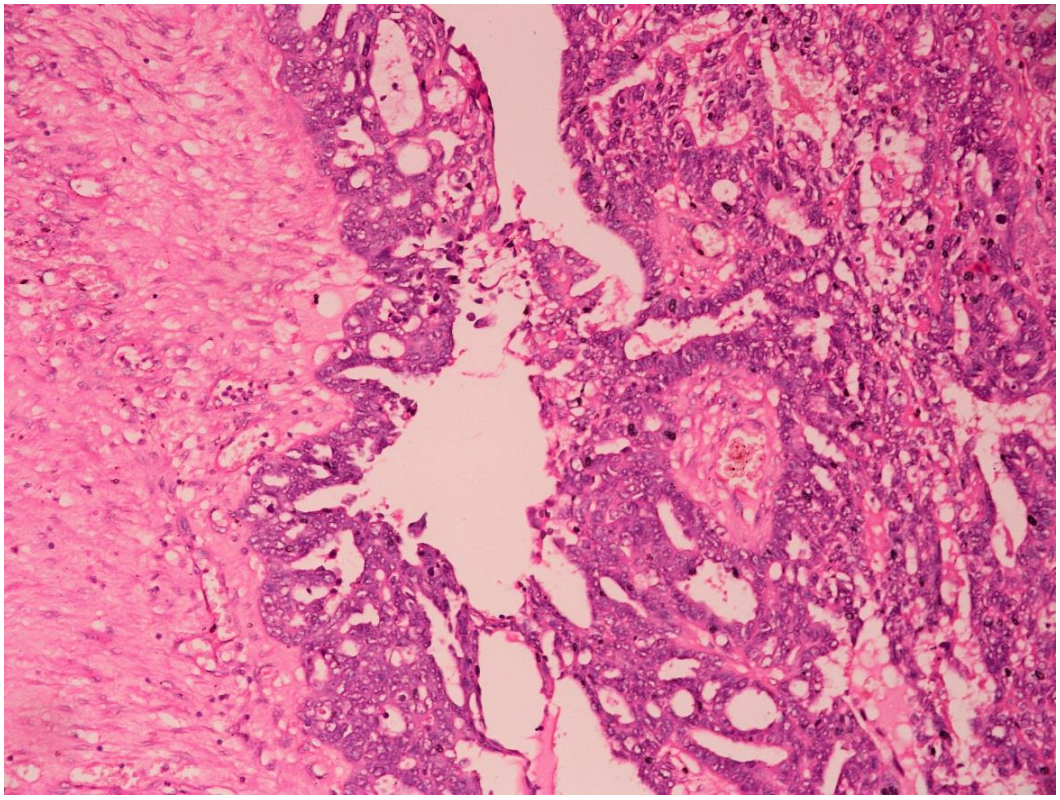

Figure 1: Malignant epithelial and stromal component is seen suggestive of malignant mixed mullerian tumour of ovary

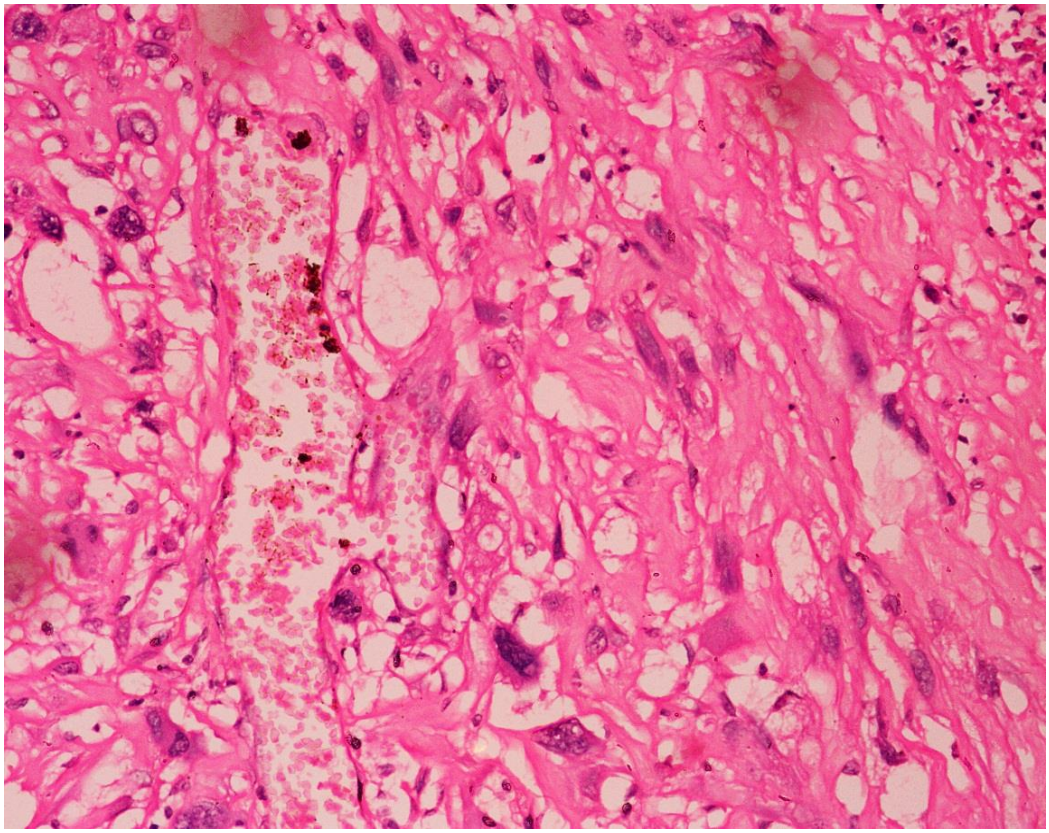

Figure 2: Pleomorphic stromal component seen,suggestive of heterologous malignant mixed mullerian tumour of ovary

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DISCUSSION

Malignant mixed mesodermal tumors(or carcinosarcomas) are rare tumors affecting the female genital tract. These aggressive neoplasms are biphasic in nature – composed of both , malignant stromal and epithelial cells.[1] Malignant mixed mesodermal tumors (MMMT) occur in the following sites in ascending order: vagina,uterine tubes, ovaries, and uterus. Peritoneum and extragenital sites may also be rarely affected.[3]

Ovarian MMMT is composed histologically of malignant epithelial and stromal elements. The epithelial components in carcinoma may be mucinous, serous, squamous, , clear cell ,endometrioid or mixture of these types and sarcomatous components, which may either be homogeneous (composed of sarcomatous elements native to the ovary) or heterogeneous (composed of malignant stromal tissue that is normally not found in the ovary such as cartilage,bone, skeletal muscle and adipose tissue).[4]Ovarian MMMT often contain cytoplasmic hyaline droplets containing alpha-1 antitrypsin.[5] In rare cases ovarian MMMT has also been found to be associated with trophoblastic tissue [5].Three main theories for histogenesis[22] of malignant mixed mesodermal tumors have been described :

- According to the collision theory the malignant epithelial and the stromal components arise independently
- According to the combination theory ,early in the evolution of the neoplasm ,a single stem cell undergoes differentiation giving rise to separate malignant epithelial and stromal component
- According to the conversion theory , metaplastic differentiation of the malignant epithelial component results in formation of the malignant stromal component.

MMMT is diagnosed post-operatively by histopathological examination and Immunohistochemical (IHC) studies. If diagnosed pre-operatively the appropriate surgical management can be planned alongwith adjuvant therapy. The diagnosis of primary ovarian MMMTs (OMMMT) is rarely suspected or confirmed preoperatively, as the clinical presentation and radiology (CT scan) is similar to ovarian epithelial tumors. These tumors are most frequently described in postmenopausal women in the 6th decade of life , Our patient is a 57 year old postmenopausal female(P_5L_4). The most common presenting symptoms are mass and pain per abdomen that were identified in our patient. However, the patient did not complain of vaginal bleeding. Patients suffering from epithelial ovarian cancer also present with similar complaints, but OMMMT is assocaiated with worse prognosis. [7]. Hb was 10 g/dl while other blood investigations were normal except CA-125 levels which were highly elevated (795 U/ml). Tumor markers such as CA-125 may be raised or may be in the normal range in OMMMT. Even cytological analysis of ascitic fluid in positive cases may yield malignant epithelial components in majority of cases(for example ,malignant adenocarcinoma in our case). The risk factors for MMMTs include nulliparity, obesity long-term tamoxifen use and exogenous oestrogen.[8]Radiation exposure is also associated with increased risk of developing OMMMT.[1]

Prognosis depends on the grade of the malignant epithelial component and the histological type and proportion of the malignant stromal component in the metastatic foci and the primary tumor. [9,10]Older age and advanced stage of tumor at time of presentation , and residual tumor after primary surgery are poor prognostic indicators .[14] In a study conducted by Athavale R *et al*, [4]statistical analysis showed that stromal predominant tumors, suboptimal debulking, age, and tumors with serous epithelial component were associated with poor prognosis. Pre-operative CA 125 levels > 75 U/ml is associated with poor prognosis.

In our case the tumor cells contained PAS+ diastase resistant cytoplasmic globules suggesting mucinous adenocarcinoma of ovary. Focal positivity for WT-1 and ER is suggestive of sarcomatous component. WT-1 is also a fairly specific marker for spindle cell tumors of gynecological organs. p53 immunostain had been reported to show positivity in both carcinomatouus and also sarcomatous areas and therefore the two components of the neoplasm might have undergone a similar carcinogenic event, with the result that carcinosarcoma can be considered to be monoclonal and originated from a common stem cell, thus supporting "combination theory".[11,12] Also,as ovarian stroma contained malignant cartilage and osteoid,we can safely say that this was a case of heterologous MMMT of both ovaries.

Because of the rarity of the disease, no standard treatment has been developed. [13] Several previous studies have found that optimal cytoreduction followed by combination chemotherapy may result in an

improved progression-free interval for patients with OMMMT. The staging and primary treatment are always surgical.[13] It has been suggested that ovarian MMMTs originate from the Mullerian epithelium and so can be managed as epithelial ovarian carcinomas.[10].Optimal cyroreduction improves survival. Chemotherapy (platinum) can prolong survival, but there are no effective second-line treatments. Radiotherapy is of no help , but has been reported to reduce local recurrence. Recurrence in MMMTs occurs in over half of patients after primary surgical and adjuvant therapy.

CONCLUSION

MMMT of ovary are usually associated with very poor prognosis , mostly due to older age and advanced stage of neoplasm at presentation. Ovarian MMMT is most often a postoperative diagnosis made by histopathological examination and immunohistochemistry of surgical specimen. Appropriate surgical management and combination chemotherapy can be optimally planned if MMMT can be diagnosed at an early stage pre-operatively. Due to rarity of this tumor, no standard treatment has been developed. It is important to develop multicenter studies involving large number of patients to improve therapeutic results.

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